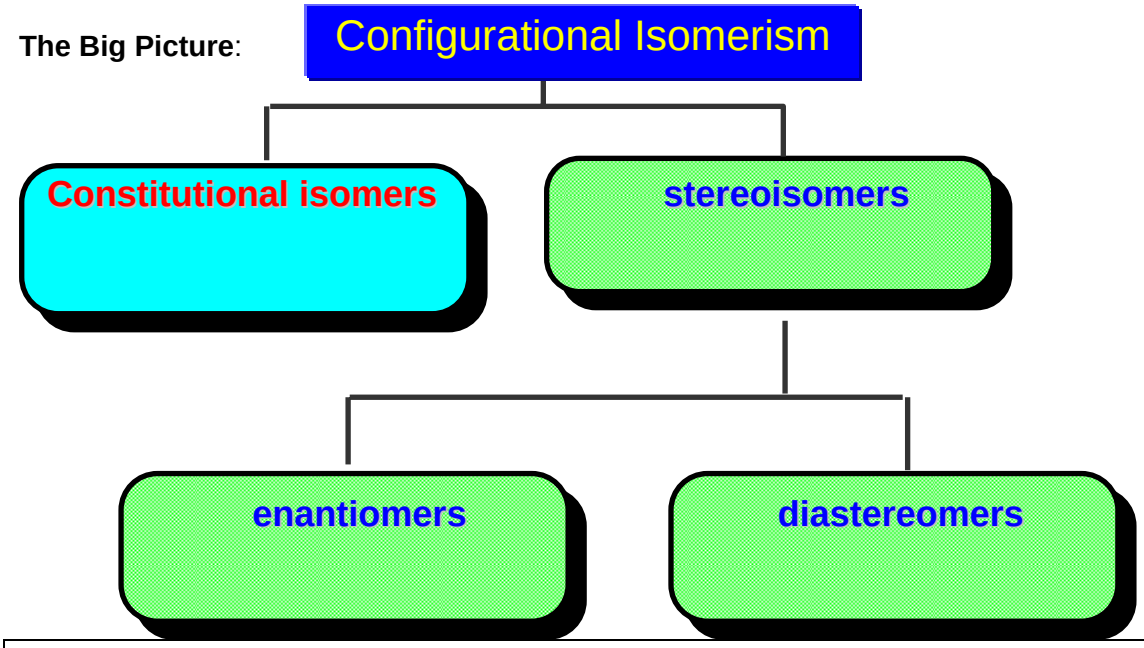
CH 9: StereoIsomerism

The Big Picture:



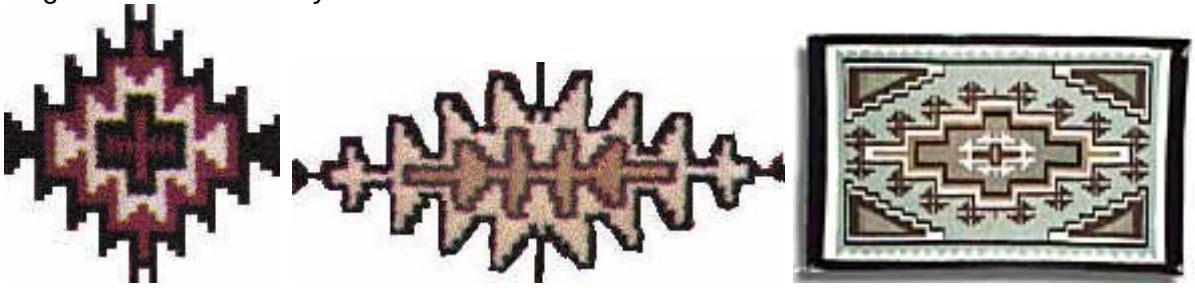
Note:
Cis/trans or E/Z are really a special case of the big picture. In the big picture, cis/trans or E/Z are referred to as geometric isomers. (special case of diastereomers).

New Perspective on StereoIsomers

The Mirror Plane

http://www.shelterpub.com/_symmetry_online/symmetry_home.html

Rug themes from nearby.



http://www.mpsaz.org/arts/elements/balance/page1.html

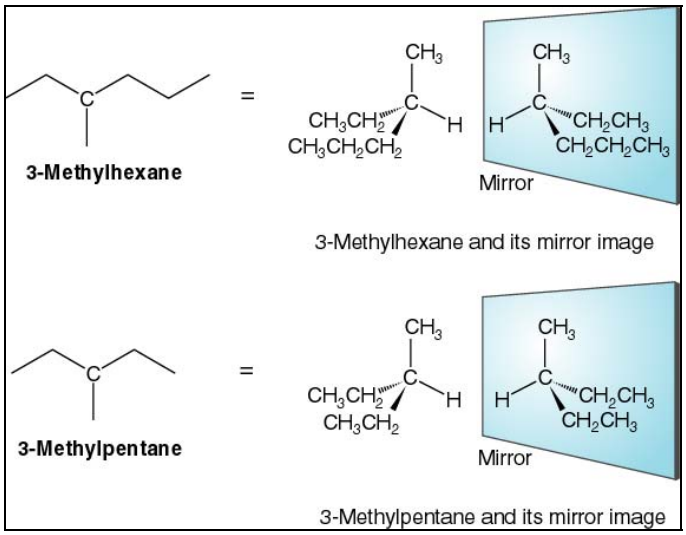

Real car Mirror?


Mirrored car?

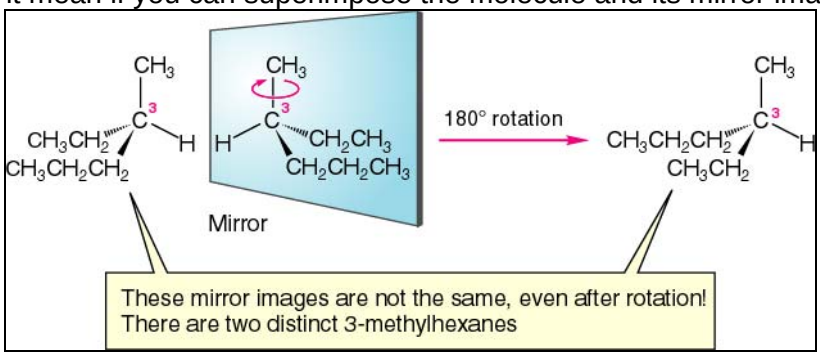

Car with(out) mirrors?

http://www.shelterpub.com/_symmetry_online/sym2_imperfect_bilateral.html

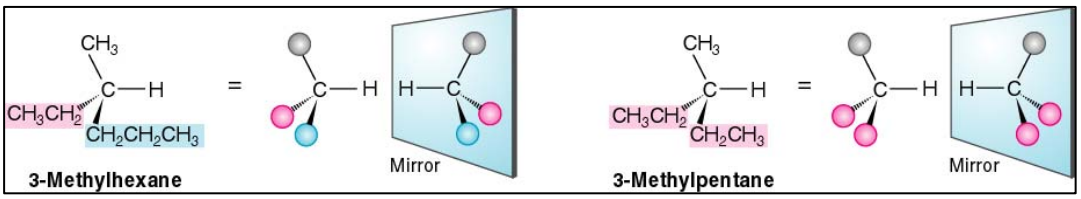
Organic Molecules have mirrors too



But what does it mean if you can superimpose the molecule and its mirror image on itself?



Here is the result.



http://www.sci.kun.nl/chemistry/onderwijs/oc1/College4.ppt

Chiral Molecules have chiral carbons

As a general rule: If the molecule is sp^3 hybrid (4 sigma bonds/attachments) and has 4 different groups, the molecule cannot be superimposed in its mirror image. This molecule is called ***chiral*** and the molecule has a ***chiral*** carbon.

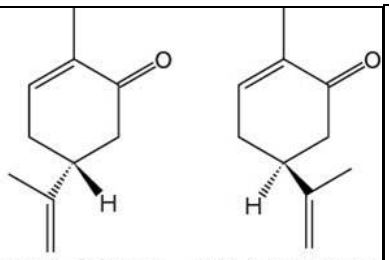
Achiral Molecules have one or more mirror planes

If the molecule has a plane of symmetry, then the molecule is not chiral, even if there are **chiral** carbons in the molecule.

Chiral Molecules with one chiral carbons have two forms The relationship between the molecules is called *enantiomers*. If there is a chiral carbon, there is usually a pair of enantiomers, like right and left hands.Here is a link with all of the terms:

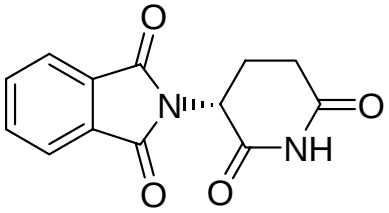
http://www.chem.qmul.ac.uk/iupac/stereo/cont.html

Enantiomers are classified as R/S and +/-.

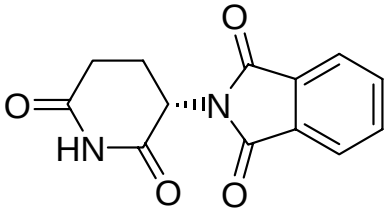


(*R*)-(–)-Carvone (spearmint)

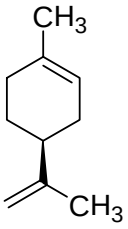
(*S*)-(+)-Carvone (caraway)



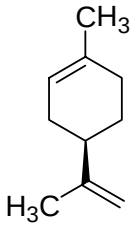
thalidomide (softenon)
(R): sedative drug



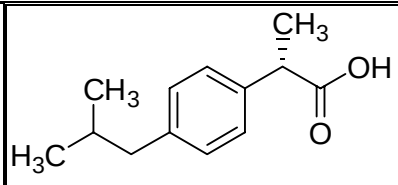
(S): teratogenic effects



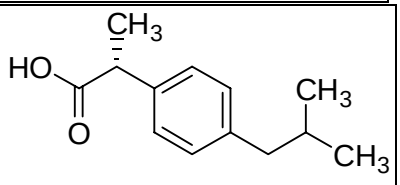
(-)-limonene
lemon odor



(+)-limonene
orange odor



(S)-ibuprofen
apirin-like activity



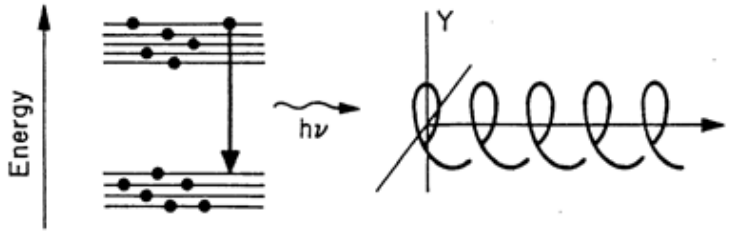
(R)-ibuprofen
slowly converted in the body into (S)-ibuprofen

http://www.sci.kun.nl/chemistry/onderwijs/oc1/College4.ppt

Designating enantiomers.

Relative Configuration (measured by experiment):

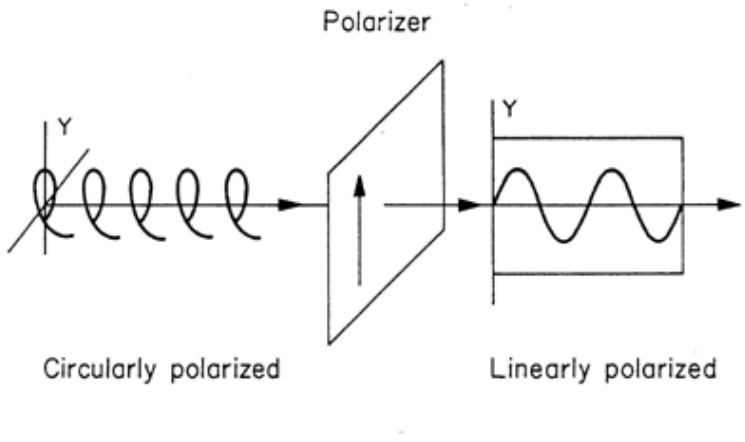
One enantiomer of a pair will have a polarity either right or left that will interact with light.
Wave nature of light results in it being circularly polarized.

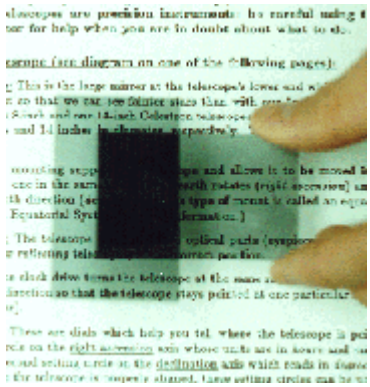


Electron energy levels

Circularly polarized emitted light

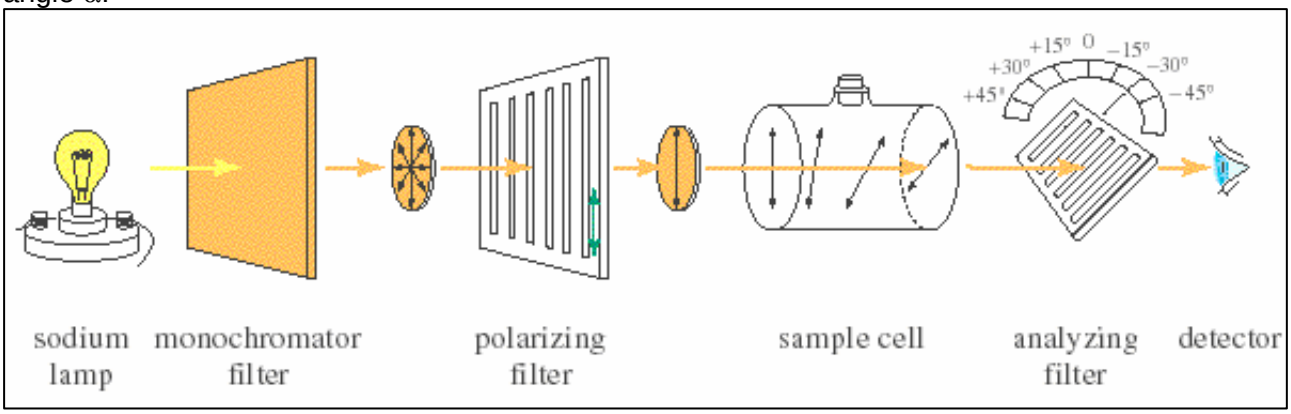
A polarizer filters out all of one plane of the polarized light and blocks the rest. Two polarizers crossed, showing a null in light transmission.





http://acept.la.asu.edu/PiN/rdg/polarize/polarize.shtml

The polarity (either right or left) of the organic molecule bends the light which is measured by the angle α.



- Rotation to the right is called dextrorotatory and abbreviated *d* or (+)
- Rotation to the left is called levorotatory and abbreviated *l* or (-)

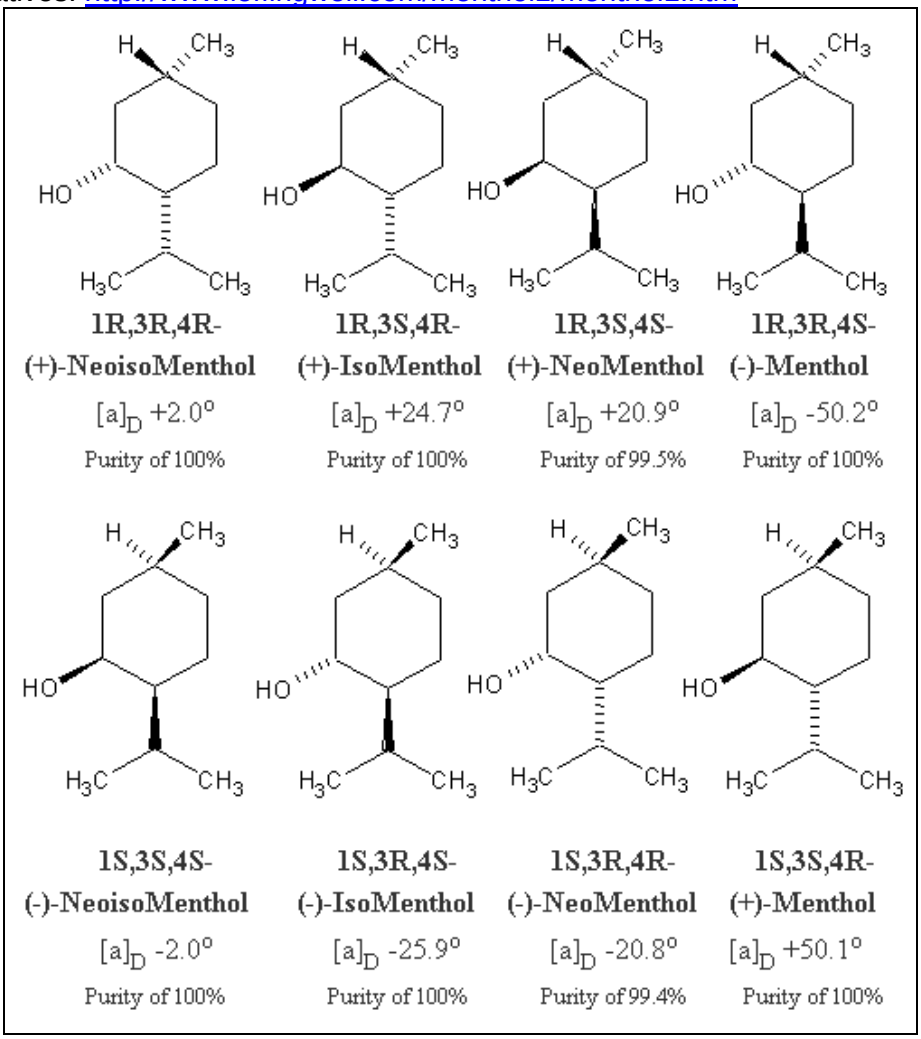
http://users.ipfw.edu/farrarj/Notes/Chapter%205.ppt

$[\alpha]_D$ = α (observed) / (concentration * length)

Specific Rotation, [α]

- 1 dm sample cell
- 1 g/mL concentration
- Usually D line of sodium lamp and 25 °C

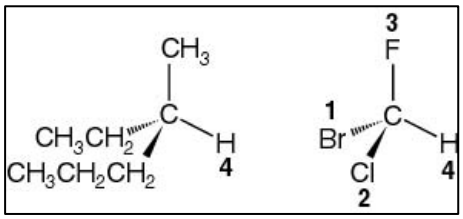
Menthol Derivatives: http://www.leffingwell.com/menthol1/menthol1.htm

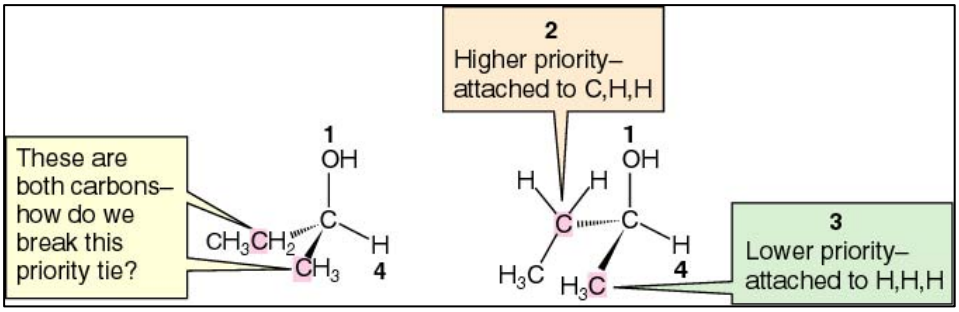


Absolute Configuration: **R/S** configuration.

1. Each point of the attachments on chiral C and assign priorities according to CIP rules.

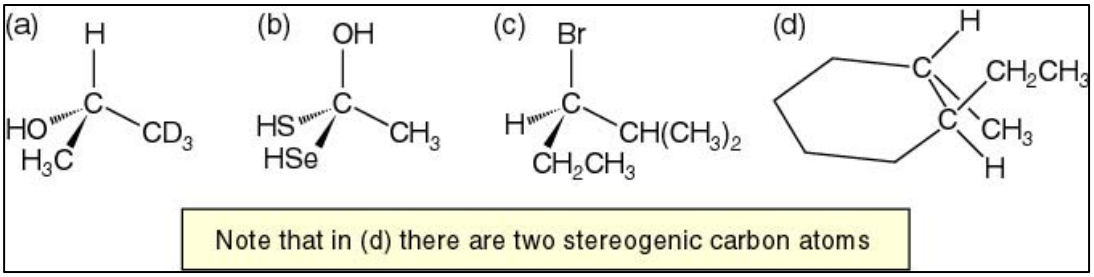
1. The higher the atomic number of the immediate substituent atom, the higher the priority. For example, H– < C– < N– < O– < Cl–. (priority increases left to right) (Different isotopes of the same element are assigned a priority according to their atomic mass.)
2. If the two substituents are the same, go to FPD (1st point of difference).
For example, CH_3– < C_2H_5– < $ClCH_2$– < $BrCH_2$– < CH_3O
3. Additions to above: C=O counts as 2 C-O bonds and C≡C counts as 3 C-C bonds.



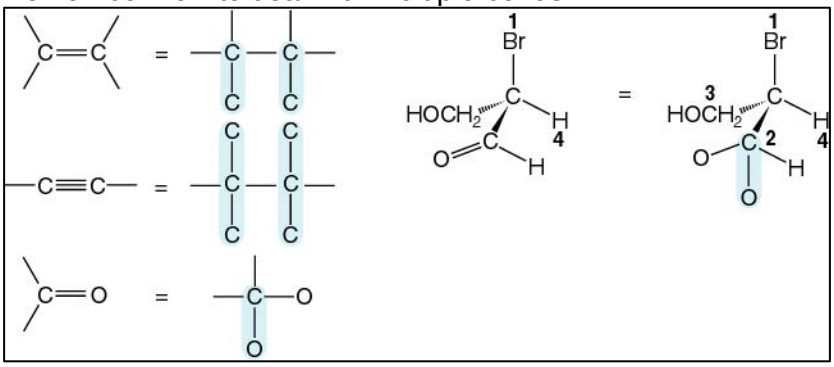


http://www.sci.kun.nl/chemistry/onderwijs/oc1/College4.ppt

Practice:



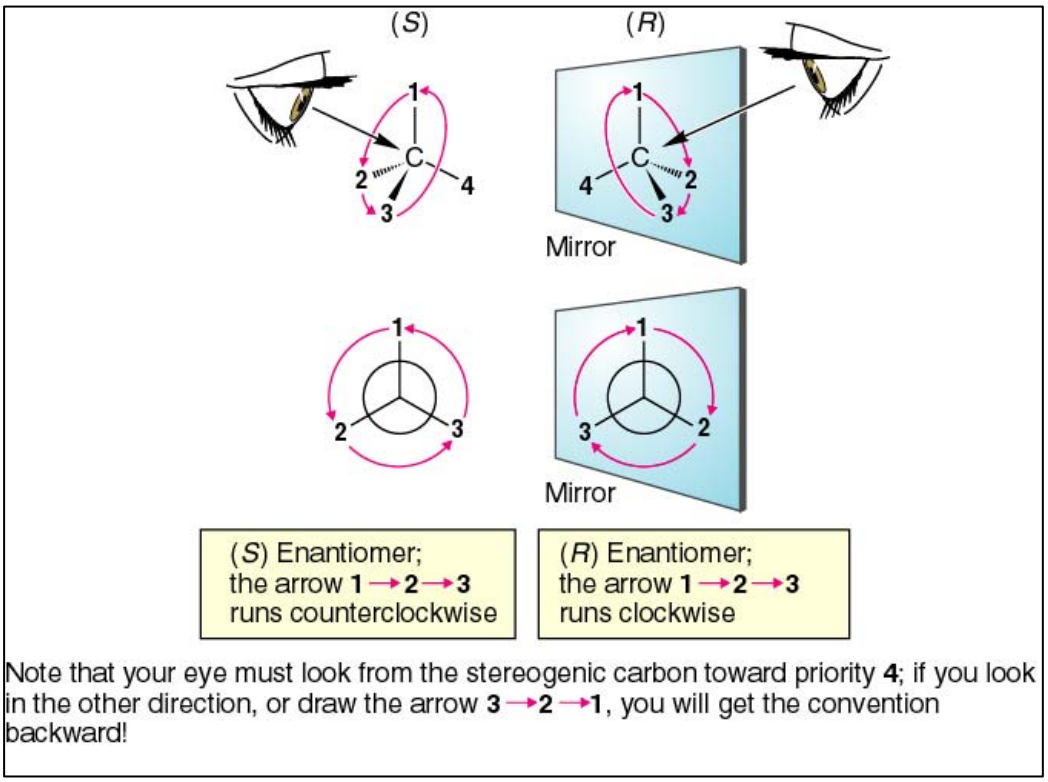
Remember how to deal with multiple bonds:



http://www.sci.kun.nl/chemistry/onderwijs/oc1/College4.ppt

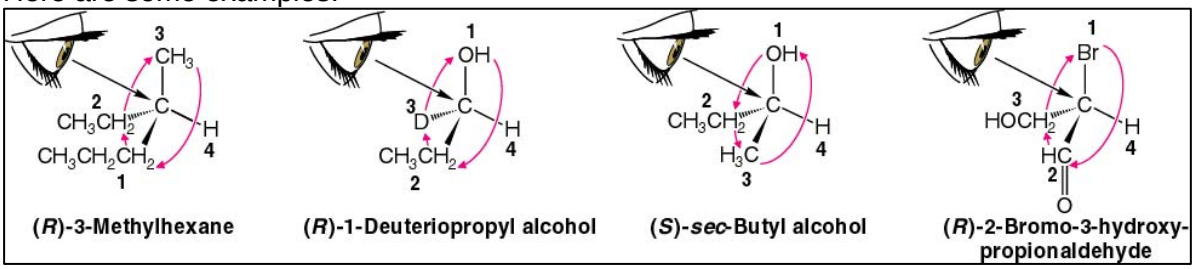
Go back to menthols and label each group. C-Me has the C1.

2. Orient the molecule so that the lowest priority group is in the back of your perspective.
   - Going down in priority runs counterclockwise: S-isomer
   - Going down in priority runs clockwise: R-isomer



http://www.sci.kun.nl/chemistry/onderwijs/oc1/College4.ppt

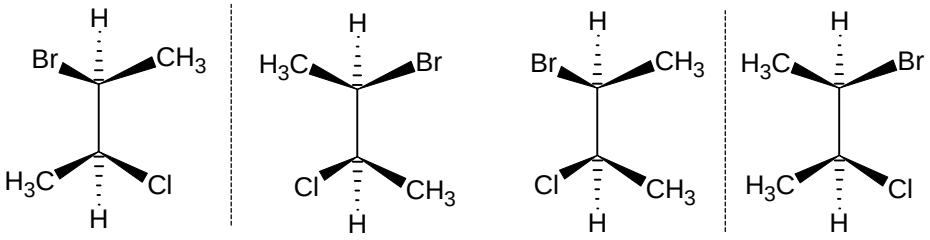
Here are some examples:



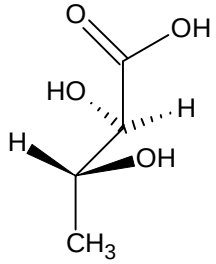
If the lowest group is not in the rear, then either
   - Rotate the molecule so that the lowest priority group is in the rear or
   - Reverse the counter- or clockwise designation.

Molecules with 2 or more chiral carbons

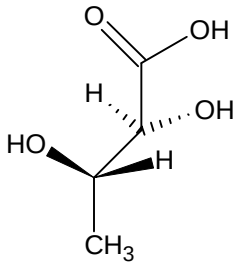
If there is no symmetry elements in the molecules, there are 2^n stereoisomers. Not all are *enantiomers*. If the molecules are not superimposable – not mirror images = *diastereomers*. Identify the relationship between these 4 isomers of 2-bromo-3-chlorobutane.



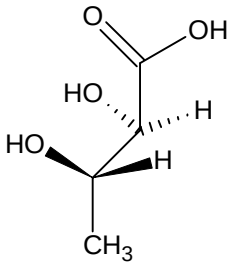
Practice: Identify R/S and enantiomers and diastereomers of 2,3-dihydroxybutanoic Acid



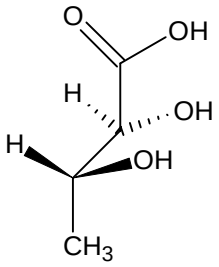
[α] = -9.5



[α] = +9.5

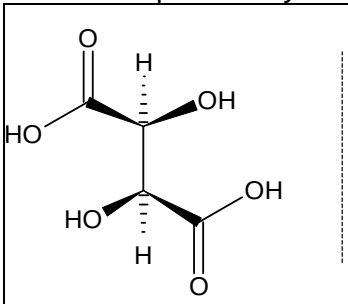


[α] = +17.8

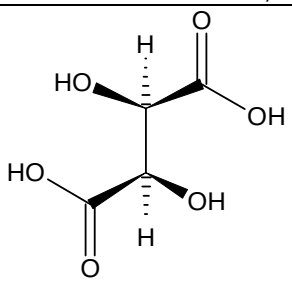


[α] = -17.8

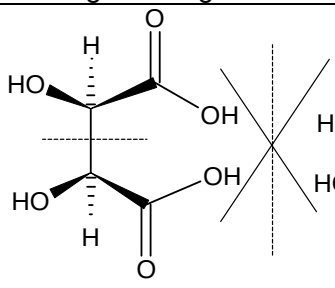
If there is a plane of symmetry in the molecule then, there is a slight change: Meso



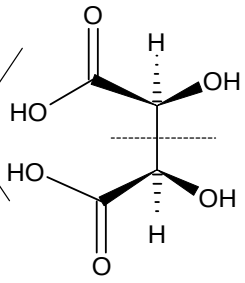
[α] = -12.3



[α] = +12.3



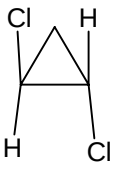
[α] = 0

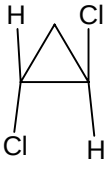


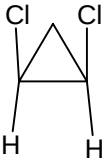
[α] = 0

How many stereoisomers here? Why is the [α] of the meso compound = 0?
Are there chiral C's in Meso compounds?

Cyclics. Assign chirality to these 1,1-dichlorocyclopropanes.







Van't Hoff's rule: Generally there are 2^n stereoisomers where n is the number of chiral carbons. Often there are less stereoisomers than 2^n. Why?

Molecular Properties

Evaluate the difference of molecular properties:

Property	Enantiomers	Diastereomers
BP		
MP		
Density		
Solubility		
Rotation of light		
Interaction with chiral substrates		

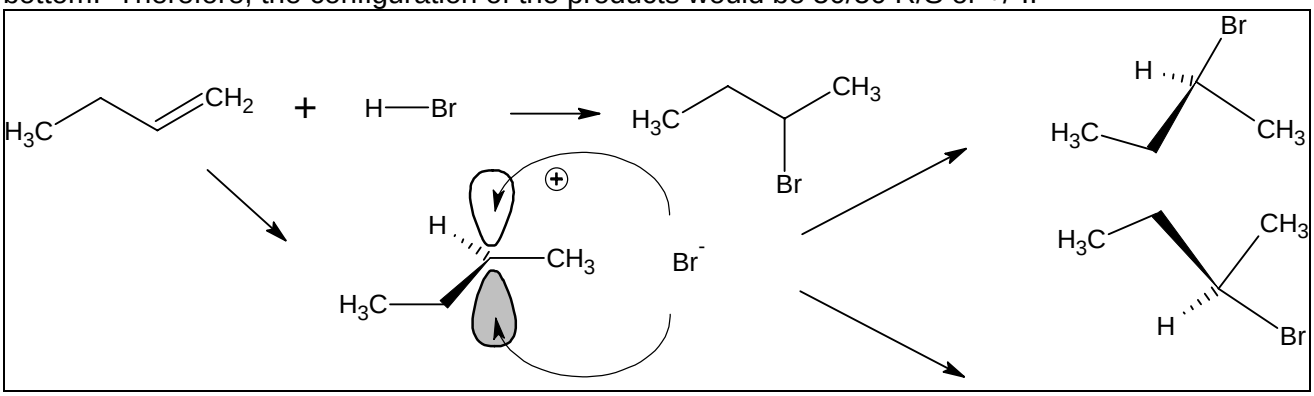
What about meso compounds?

Reactions and Stereochemistry

In general, it takes something chiral to make something chiral.
It depends on mechanism.

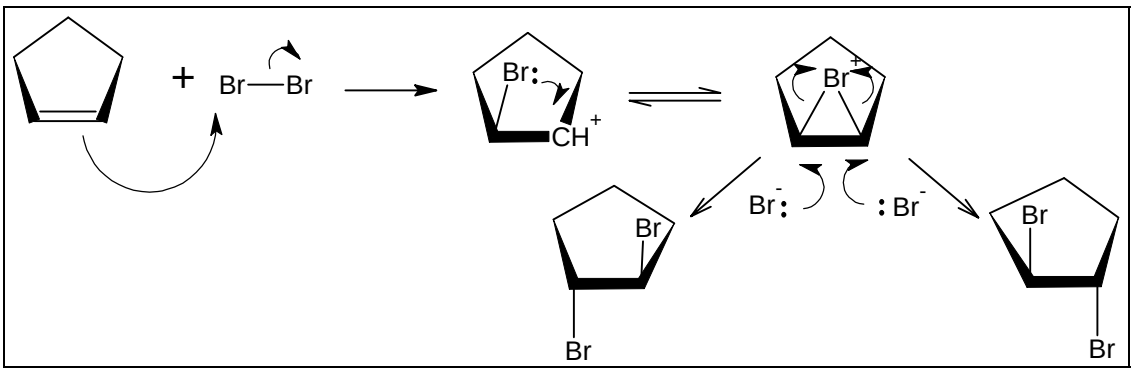
Electrophilic Addition

In the C+ intermediate, there is roughly 50/50 chance of the Br:$^-$ coming in from the top or the bottom. Therefore, the configuration of the products would be 50/50 R/S or +/-..



Are the products overall chiral?
Nature's way of getting back for the formation of chiral products from achiral reactants.
This is called the ***racemic*** mixture.

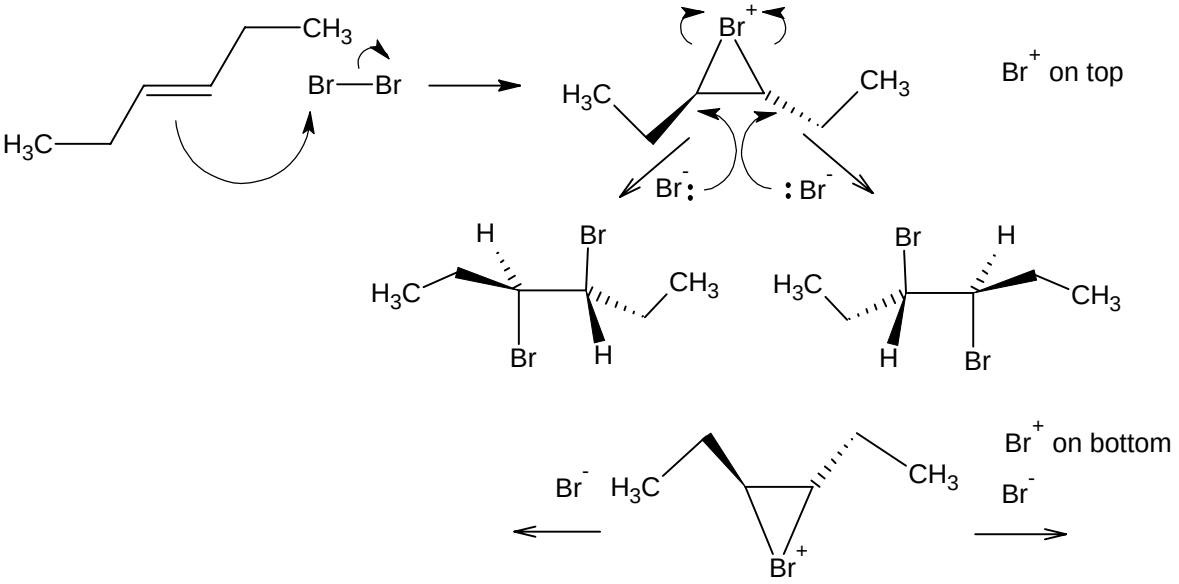
Anti-Addition of Br_2



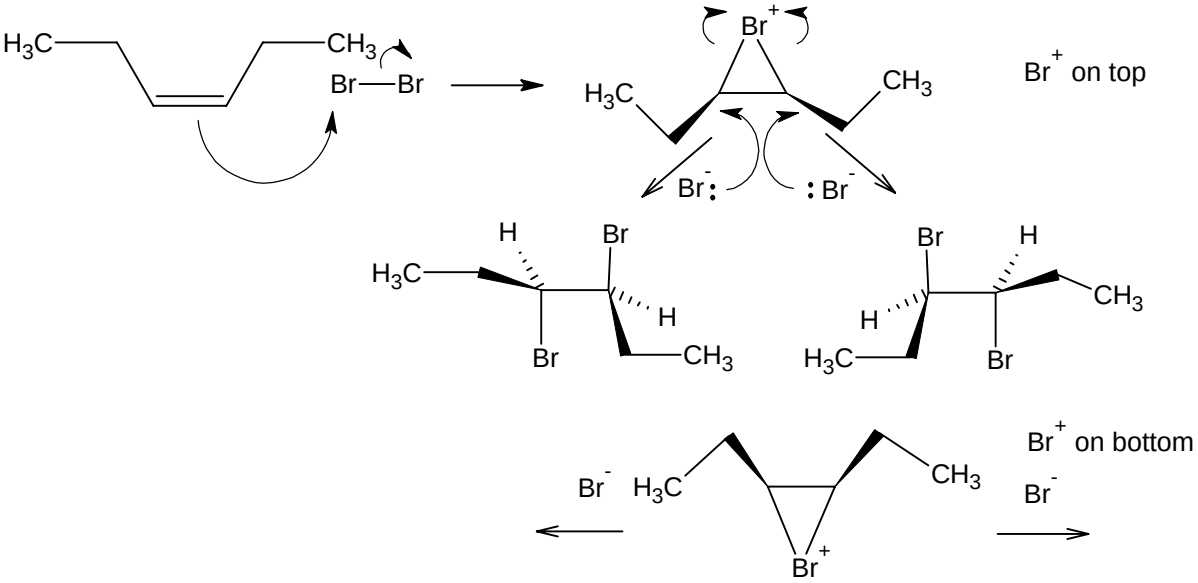
What is the relationship between these two trans products.
Is the reaction chiral overall?

Now consider the addtition of Br_2 to cis and trans alkenes.

trans 3-hexene

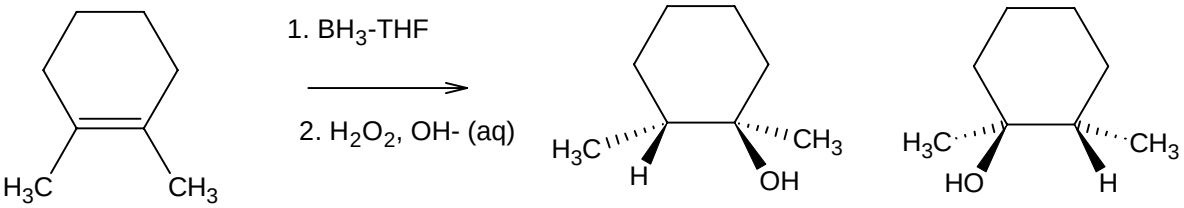


cis 3-hexene



Other anti additions: HOBr and HOCl

Hydroboration of alkenes



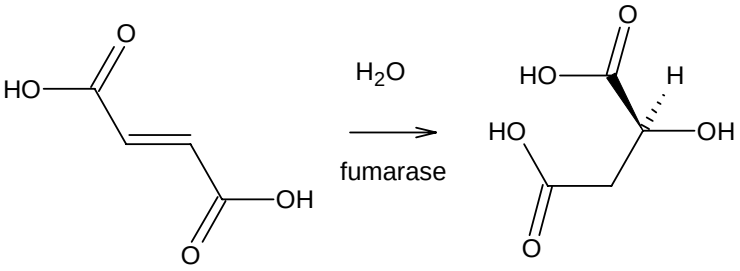
What is the relationship and quantity of the products?

Review Pt catalyzed syn addition of H_2 or even D_2"

Review syn addition of OsO_4 to an alkene.

Review carbenoids additions.

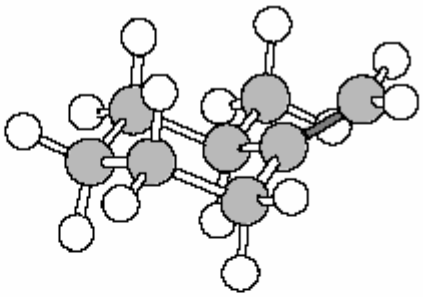
Biosynthesis and chiral enzymes

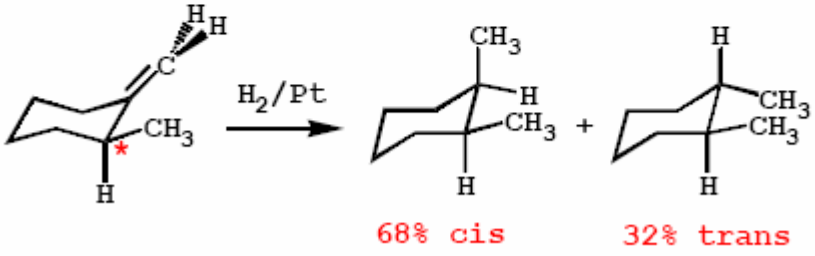


fumaric acid - achiral (S)-(-)-malic acid -- single product

Asymmetric Induction and Enantiomeric Excess

unsymmetrical alkene → (top & bottom of C=C are different)



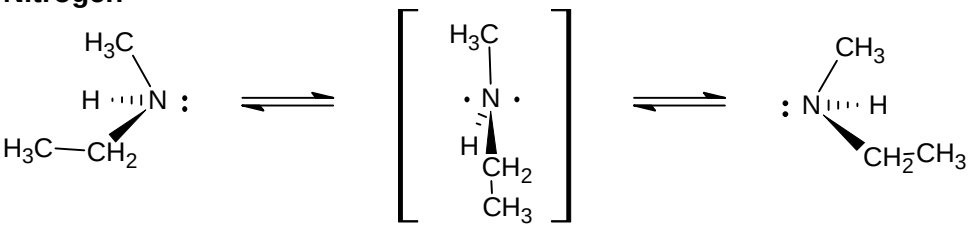


http://www.chem.umd.edu/courses/chem233/chapterspdf/main9-pages-pdf.pdf

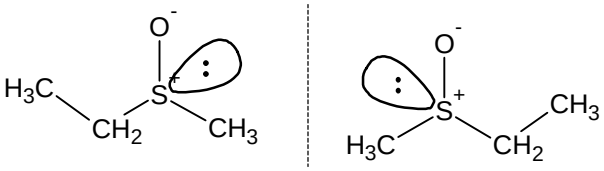
The % of enantiomeric excess is equal to %(major) - %(minor).
For racemic mixture, the enantiomeric excess = ?
Above, the major product of the reduction of the chiral alkene was 68% RS and the minor product was 32% SS, what would be the diastereomeric excess?

Many catalysts are being developed that are chiral to induce asymmetry in the reaction. This approach led to the Nobel prize in chemistry in 2001. See the drug analysis at the end.

Nitrogen

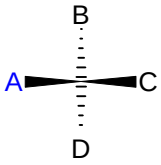


Sulfoxide

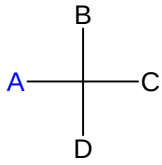


Fischer Projections and Sugars

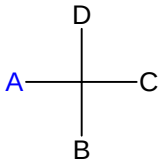
Horizontal Orientation



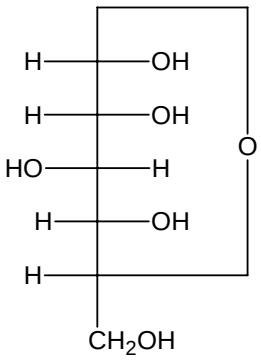
Tetrahedral Carbon (dash/wedge)



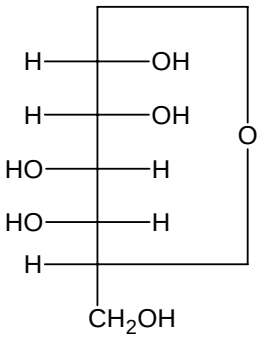
Fischer Projection



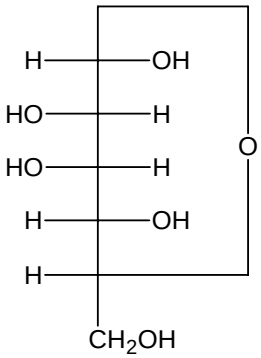
180 degree turn OK



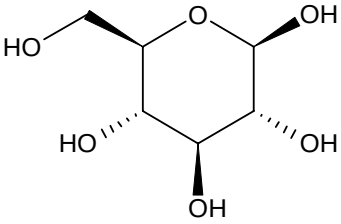
D-Glucose

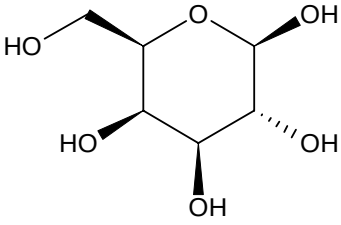


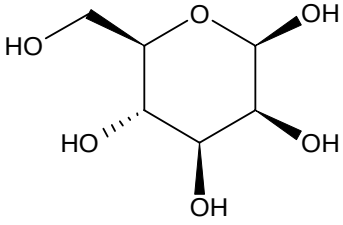
D-Galactose

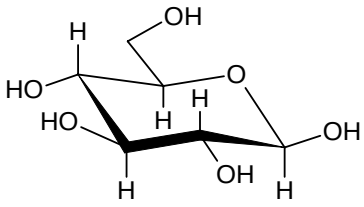


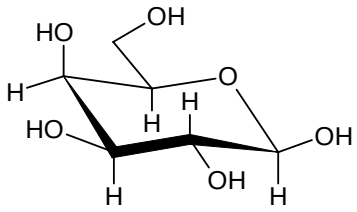
D-Mannose

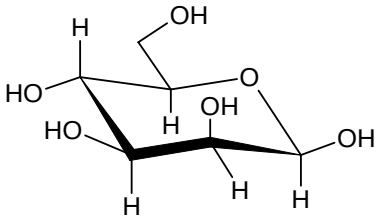




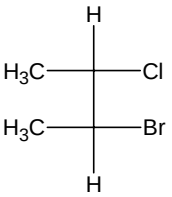


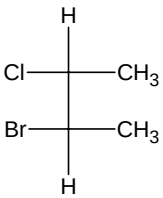


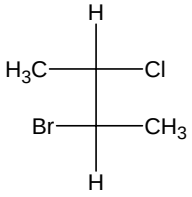


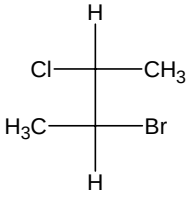


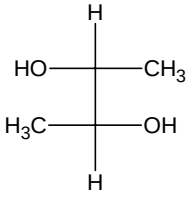
Assign R/S of these Fischer Projections

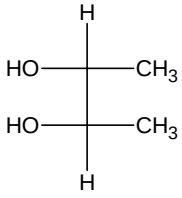




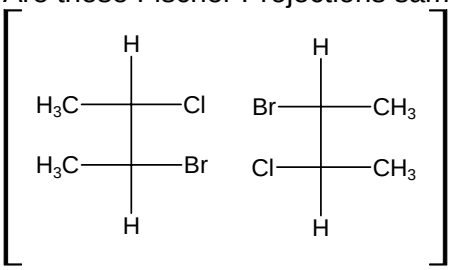


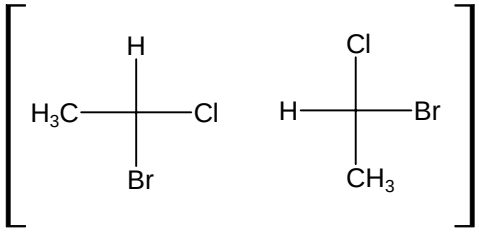




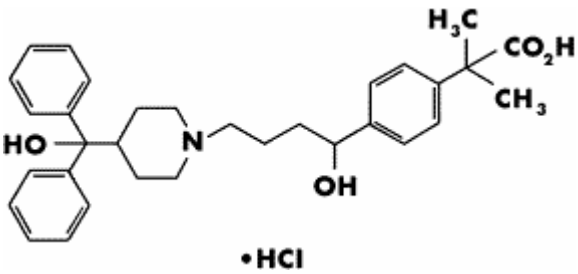


Are these Fischer Projections same or different?





Allegra - DESCRIPTION *Fexofenadine hydrochloride,* the active ingredient of **ALLEGRA**®, is a histamine H_1-receptor antagonist with the chemical name (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl) -1-piperidinyl]-butyl]- alpha,alpha-dimethyl benzeneacetic acid hydrochloride.



The molecular weight is 538.13 and the empirical formula is: $\mathbf{C_{32}H_{39}NO_4 \bullet HCl}$.

Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at physiological pH.

ALLEGRA is formulated as capsules for oral administration. Each capsule contains 60 mg fexofenadine hydrochloride and the following excipients: croscarmellose sodium, gelatin, lactose, microcrystalline cellulose, and pregelatinized starch. The printed capsule shell is made from gelatin, iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and other ingredients.

Allegra Home • Site Map
Hoechst Marion Roussel USA Home

http://madang.ajou.ac.kr/~ydpark/archive/allergy/antihistamines.htm

In 1992, for instance, the FDA ordered Merrell Dow, which later became part of Aventis, to put a warning label on its allergy drug terfenadine (Seldane) after adverse reaction reports began pouring into the agency. Doctors who prescribed the nonsedating antihistamine for their allergy patients reported many terfenadine users had suffered severe heart palpitations after taking the drug. Six years and at least eight deaths later, it was withdrawn from the market. But the drug was resuscitated when a specialty chemical company called Sepracor separated the two enantiomers of terfenadine for Aventis, which was then able to continue marketing the safe but active half. They called it Allegra. Sepracor later performed the same trick for Johnson and Johnson after its allergy drug astimezole (Hismanal) suffered a similar fate.
http://www.ucpress.edu/books/pages/10083/10083.ch08.html
Merrill Goozner **The $800 Million Pill** *The Truth behind the Cost of New Drugs*

Outside the top 10, some individual products registered impressive growth rates, led by Nexium, AstraZeneca's replacement for Prilosec. Like a number of new products, Nexium is an isomer of Prilosec, designed to be safer, faster acting, and more effective. Many drugs are administered in a racemic form; that is, a mix of chiral isomers. Often, only one isomer is responsible for the drug's efficacy and the other may be responsible for undesirable side effects. Other isomeric drugs include Lundbeck & Forest's Cipralex/ Lexapro (Cipramil/Celexa), as well as Schering-Plough's Clarinex (Claritin) and Aventis' Allegra (Seldane) antihistamines, both of which were developed by specialty company Sepracor.

After Prilosec's basic patents expired in the U.S. in October 2001, AstraZeneca dedicated huge resources to launching and establishing Nexium in the marketplace. It appears to have been successful, as Nexium accounted for more than 20% of new prescriptions in the proton pump inhibitor market by October 2002, having been launched in March 2001.
It is yet to be seen, however, how successful these marginally superior products will be when the originals lose exclusivity or move to nonprescription OTC status, both of which could happen with Claritin before the end of 2002. Some U.S. insurance companies have already said they will not cover the routine use of the new, more expensive products if an older, tried-and-tested drug is available as a cheaper generic.
http://pubs.acs.org/cen/coverstory/8048/8048pharmaceutical.html

Nexium and Prilosec

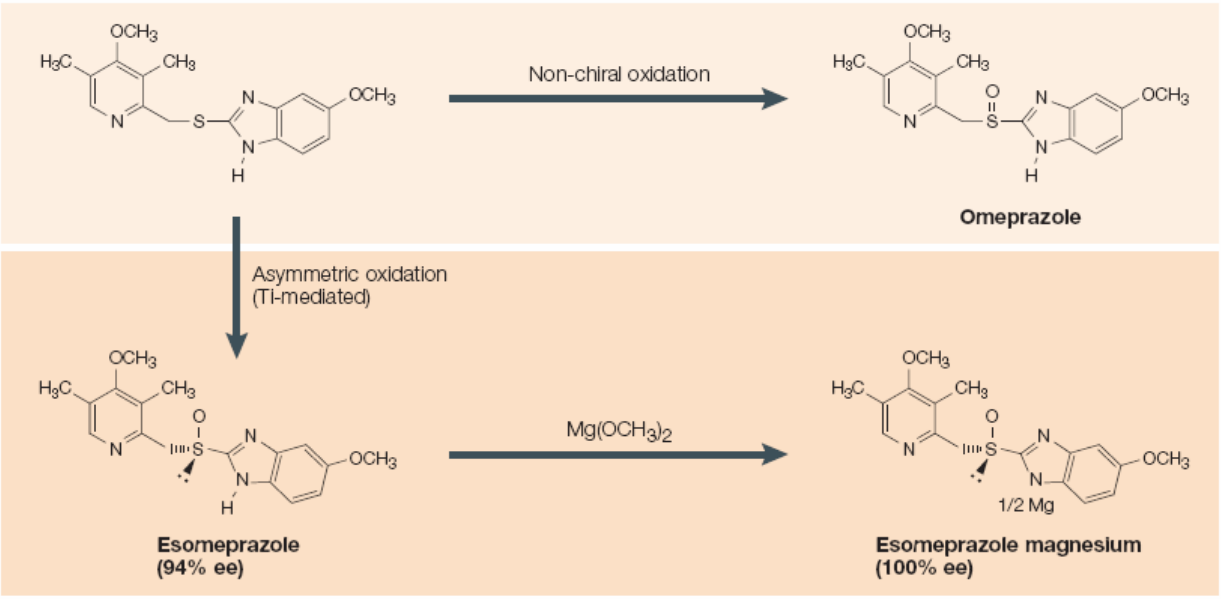


Figure 3 | **Synthesis of omeprazole and esomeprazole.** The large-scale production of esomeprazole is achieved by asymmetric oxidation of the same sulphide intermediate as is used in the production of omeprazole, which gives a 94% enantiomeric excess (ee). This is increased to 100% by preparing a magnesium salt of of esomeprazole and then performing a crystallization.

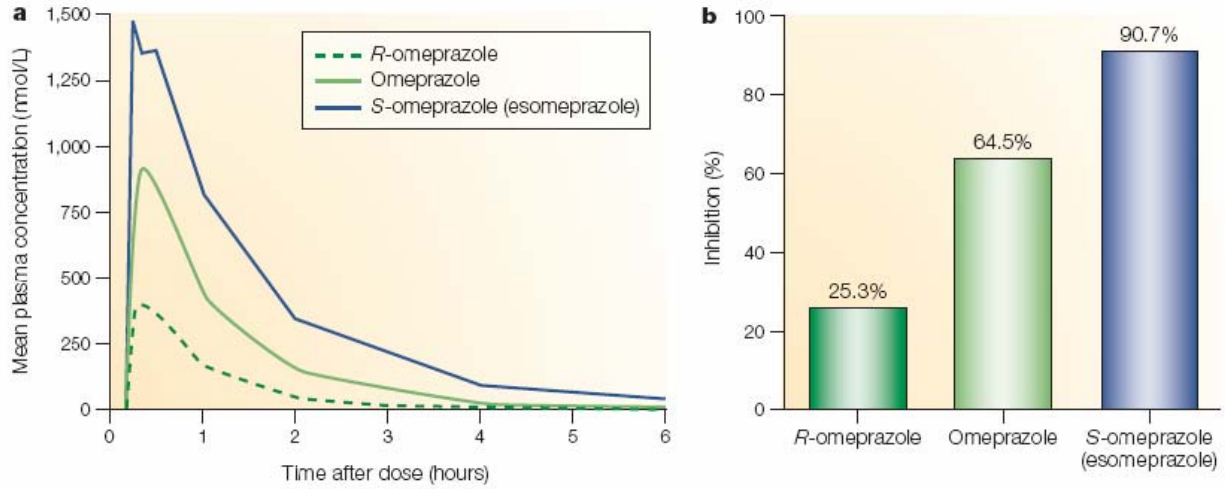


Figure 4 | **Effects of racemic omeprazole and its enantiomers. a** | Drug plasma concentrations and **b** | inhibition of pentagastrin-stimulated gastric acid secretion in healthy subjects ($n = 4$) after oral administration of 15 mg of *R*-omeprazole, omeprazole and esomeprazole at time 0 (REF. 42).

http://www.chem.missouri.edu/GatesGroup/Prilosec.pdf

Many pharmaceuticals and psychoactive drugs depend on specific chiral interactions. See
http://www.leffingwell.com/download/chirality-phamacology.pdf

Resolution of Enantiomers

Basic Strategy

(R)-molecule ⇆ (S)-molecule Enantiomers cannot be separated

If the two enantiomers.are complexed with a chiral reagent (enzyme, salt, or column material), what is the relationship between these complexes with a hypothetical chiral reagent R.

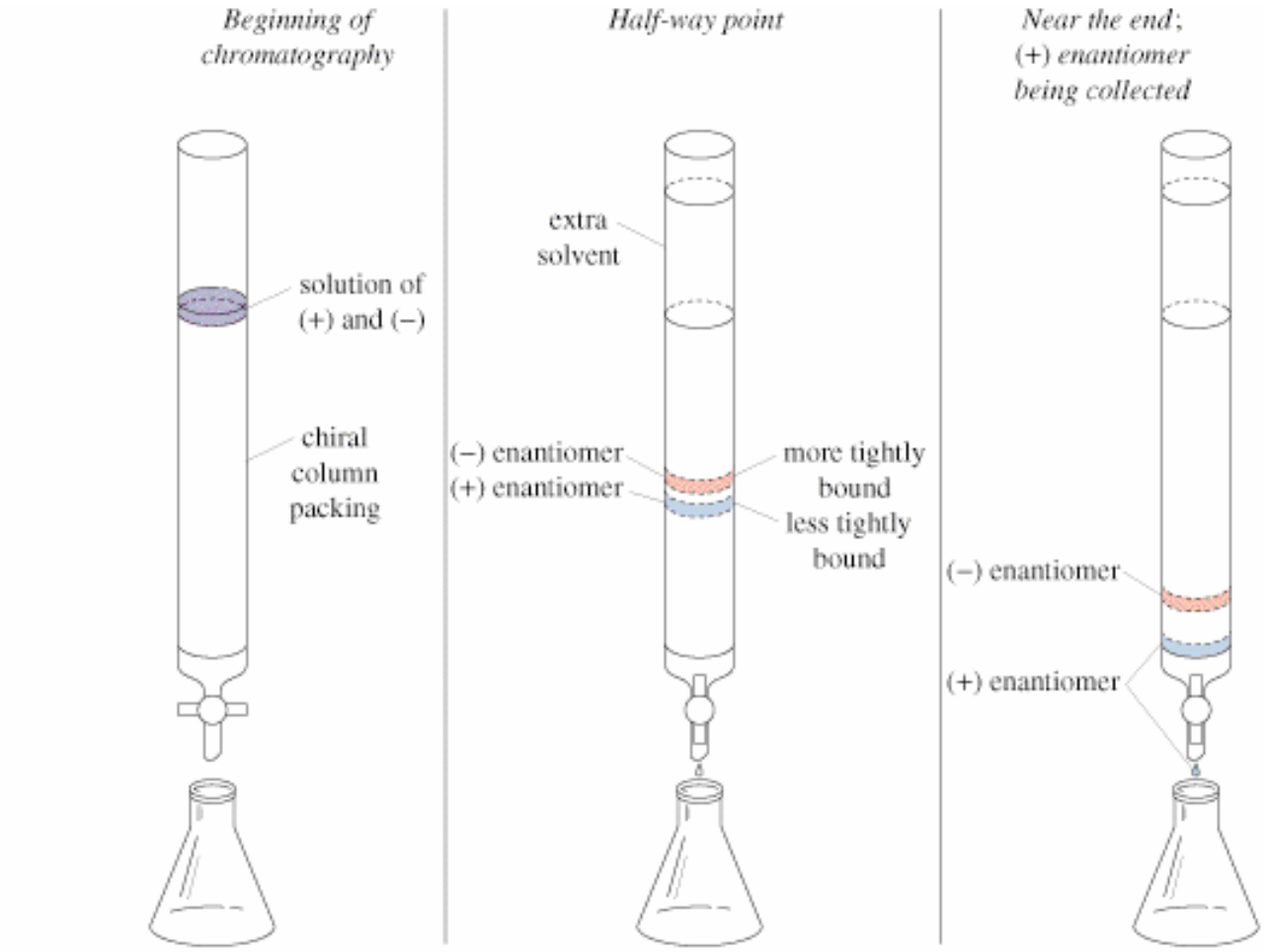
(R)-molecule + (R)-Reagent ⇌ (R)—(R) → separate → (R)—(R) ⇌ (R)-molecule + (R)-Reagent

(S)-molecule + (R)-Reagent ⇌ (S)—(R) → separate → (S)—(R) ⇌ (S)-molecule + (R)-Reagent

Enantiomers cannot be separated ?

"It takes something chiral to make something chiral!"

Here is a schematic of how a chiral chromatography column might work. What is the principle of chromatography?



Graphic above used without permission from
http://users.ipfw.edu/farrarj/Notes/Chapter%205.ppt